Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Fertility rates and birth outcomes after ChAdOx1 nCoV-19 (AZD1222) vaccination

Fears of adverse effects of COVID-19 vaccination on fertility have affected vaccine uptake in some communities. Despite the absence of supporting evidence for such a risk, low biological plausibility, and preliminary data supporting the safety of mRNA vaccines in pregnancy,[1–3] this claim has become widespread, and it has been challenged by WHO.[4] Vaccine hesitancy during pregnancy, or among women of childbearing age, could have substantial public health consequences because infection with SARS-CoV-2 during pregnancy is a risk factor for severe maternal illness and complications.[5,6]

We have analysed pregnancies that have occurred in four ongoing phase 1, phase 2, and phase 3 clinical trials of ChAdOx1 nCoV-19 (AZD1222)[7] in three countries (NCT04324606 and NCT04400838 in the UK; NCT04536051 in Brazil; and NCT04444674 in South Africa). Participants of childbearing age (defined as 49 years or younger) were randomly assigned to receive ChAdOx1 nCoV-19 or the control vaccine. Pregnancy was an exclusion criterion in all four trials, and all female volunteers tested negative for urine β-hCG before vaccination. Any pregnancies that occurred after vaccination were recorded and followed up until 3 months after birth. Pregnancy outcomes were reviewed by the independent data and safety monitoring board.

121 (1%) of 9755 participants reported a pregnancy during the trials. The fertility outcome analysis set included 93 pregnant women, 50 of whom received ChAdOx1 nCoV-19, and 43 of whom received the control vaccine. The pregnancy outcome analysis set included 107 women, 72 of whom received ChAdOx1 nCoV-19, and 35 of whom received the control vaccine (appendix p 1). Miscarriage was defined as pregnancy loss before 23 weeks of gestation. Baseline characteristics were similar between the vaccine and control groups, with the biggest differences being age and current alcohol use (appendix p 2).

We found no evidence of an association between reduced fertility and vaccination with ChAdOx1 nCoV-19 (p=0·53–0·80; table 1; for fertility rates by site, see appendix p 3). Analysis of pregnancy outcomes (table 2) excluded women in the control vaccine groups who had received either ChAdOx1 nCoV-19 or an mRNA vaccine as part of a national vaccine roll-out programme (n=14, including 11 women vaccinated after unmasking and during pregnancy (table 1), plus three additional women who received an mRNA vaccine before pregnancy; appendix p 2). 56 (52%) of 107 pregnancies in the pregnancy outcome analysis set were ongoing at the time of data lock on July 1, 2021.

Notably, the rate of miscarriage was no higher in the ChAdOx1 nCoV-19 group than in the control group, with a risk ratio (RR) of 0·67 (p=0·51). Adjusting the analysis for the effect of possible confounders kept the RR below but closer to unity at 0·84 (appendix p 4). 15 livebirths had taken place by the time of the analysis, and the three preterm births in the ChAdOx1 nCoV-19 group were in the late preterm stage (34–37 weeks of gestation). No stillbirths or neonatal deaths were reported in either group.

No terminations of pregnancy were reported in Brazil. However, termination of pregnancy is illegal in Brazil, and uncertainty remains about whether the reports of early pregnancy losses were all miscarriages. Therefore, a combined analysis of either miscarriage or termination was done for all sites (table 2), with separate subgroup analyses for termination alone and for miscarriage alone, excluding the Brazilian data. This subgroup included 24 participants who received a control vaccine and 43 participants who received ChAdOx1 nCoV-19.

Fertility was unaffected by vaccination with ChAdOx1 nCoV-19. Furthermore, compared with women who received the control vaccine, there was no increased risk of miscarriage and no instances of stillbirth in women vaccinated before pregnancy in global clinical trials of ChAdOx1 nCoV-19.

With increasing availability of misinformation, which continues to affect vaccine uptake, these data, along with published data on mRNA vaccines,[2,3] can provide evidence to support women in making decisions regarding vaccination.

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19 (AZD1222). AJP is chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation but does not participate in its discussions on COVID-19 vaccines, is a member of the WHO Strategic Advisory Group of Experts on Immunization, and a UK

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See Online for appendix

	ChAdOx1 nCoV-19 (n=4925)	Control (n=4830)*	Fertility rate ratio (95% CI)	p value
Pregnant women (fertility rate)†	50 (0·0102)	43 (0·0089)	1·14 (0·76–1·71)	0·53
Viable pregnancies (fertility rate)‡	32 (0·0065)	29 (0·0060)	1·08 (0·66–1·79)	0·80

Data are n (fertility rate) unless otherwise stated. *11 women vaccinated during pregnancy were included in the controls (eight received AZD1222 and three mRNA vaccines). †28 pregnant women (six in the control vaccine group and 22 in the AZD1222 group) were excluded from this fertility analysis because they were unmasked to vaccine allocation before becoming pregnant. ‡Viable pregnancies did not include pregnant women who had a termination or miscarriage.

Table 1: **Fertility rates**

	ChAdOx1 nCoV-19 (n=72)	Control (n=35)	Risk ratio (95% CI)	p value
Miscarriage, excluding Brazilian data	6/43 (14%)	5/24 (21%)	0·67 (0·23–1·97)	0·51
Termination, excluding Brazilian data	8/43 (19%)	6/24 (25%)	0·74 (0·29–1·89	0·55
Miscarriage or termination, all	23/72 (32%)	13/35 (37%)	0·86 (0·50–1·49)	0·67
Preterm birth	3/10 (30%)	0/5 (0%)	Not calculable	0·51*
Full-term birth	7/72 (10%)	5/35 (14%)	0·68 (0·23–1·99)	0·52
Ongoing pregnancy	39/72 (54%)	17/35 (49%)	1·12 (0·75–1·67)	0·68

Data are n/N (%) unless otherwise stated. *Two-sided p value.

Table 2: **Pregnancy outcomes**

National Institute for Health Research senior investigator. All other authors declare no competing interests. The members of the Oxford COVID Vaccine Trial Group are listed in the appendix (pp 5–19).

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Blood pressure treatment: how low should you go?

Kazem Rahimi and colleagues[1] report a participant-level meta-analysis of 48 randomised trials and conclude that lowering systolic blood pressure (SBP) reduces risk of major cardiovascular events, independent of baseline SBP. We very much agree with their recommendation to use risk prediction tools when making treatment decisions, but have the following questions about the analysis.

Although the authors describe a desire to standardise benefit according to the degree of blood pressure lowering, why did the analysis forgo use of participant-level SBP change from baseline in favour of a trial-level variable (ie, a between-group mean difference in achieved SBP, in units of 5 mm Hg)? An analysis using individual participant-level SBP changes can still report hazard ratios on a per 5 mm Hg basis.

Not all trial participants would have obtained the same degree of blood pressure lowering from a given therapy, and individual blood pressure responses might have been an important predictor of outcomes. Would the results have differed in the subgroup of participants with the lowest baseline SBP (ie, <120 mm Hg), who had the largest reductions in SBP? Without use of participant-level SBP data, such important nuances could have been unaccounted for.

Given the clinical implications of this study and the large number of normotensive individuals who could now be offered blood pressure lowering therapy on the basis of these findings, we encourage the authors to consider substantiating their results by repeating the same analysis using each participant's own change in SBP from baseline.

We declare no competing interests.

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Authors' reply

We thank Scott R Garrison and James McCormack for their interest in our study and for raising important questions concerning the study methodology.[1]

We have considered individual participant-level blood pressure changes in our analyses. In a separate investigation, we used repeated blood pressure measurements for each individual to model changing differences in blood pressure longitudinally.[2] This modelling ensures that we apply the same method to all studies, and consider differences in follow-up duration and frequency of re-measurements over time. We then used these modelled, temporal blood pressure values for individuals to calculate group-level differences between treatment groups for each trial. These estimated differences for each trial were used to standardise the randomised effects on outcomes (expressed per 5 mm Hg difference in systolic blood pressure). By weighting the effects on the basis of the average change in blood pressure between randomised groups in a trial, we adhere to the intention-to-treat principle of comparisons and leverage the individual-level information that helps to increase the precision of the estimates.

It could be argued that using trial-level average differences in blood pressure between treatment groups assumes that blood pressure changes are similar among subgroups with different clinical characteristics, where in reality they might have responded differently to treatment. In our earlier investigation, we explored this question and assessed the effects of treatment on blood pressure changes by age, sex, past medical history, previous use of antihypertensive drugs, and baseline blood pressure.[2] Although there were some variations in blood pressure reduction among subgroups, blood pressure lowering treatment was effective in reducing blood pressure across all strata of characteristics that